REMARKS

Applicants wish to thank the Examiner for the courtesy extended to the Applicants' representatives and one of the inventors by granting a personal interview. As a result, Claim 1 has been amended. Support for the amendments can be found in the Specification as filed (see, paragraph [0054] of the Substitute Specification) and in Claim 10 as originally filed The following addresses the substance of the Office Action.

Non-obviousness

The Examiner has rejected Claims 1, 2, 9, 10, 12, 13, 16, 17, 38, 40, 42, 44 and 45 under 35 USC §103(a) as being allegedly unpatentable over Guschin et al. (*Appl. Environ. Microbiol.* 1997 63:2397-2402) in view of Bamdad et al. (USP 6,541,617). More specifically, the Examiner alleges that it would have been obvious to one skilled in the art at the time the invention was made to modify the method of Guschin et al. by using a spacer of at least 40 bases in length as taught by Bamdad et al.

> To establish a *prima facie* case of obviousness, the PTO must cite one or more references that provide some suggestion or motivation to modify the references to achieve the claimed invention, provide a reasonable expectation of success to achieve the claimed invention, and finally, the cited art must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Here, the cited art either taken alone or in combination, fails to provide any of the required factors.

As discussed in the Inventor's Declaration filed herewith under 37 C.F.R §1.132, the inventors' goal was to find the best standard conditions for identifying a nucleotide sequence. among several homologous sequences with homology higher than 30% against at least four other sequences. The inventors tested the effects of the length of the target molecules, the length of the capture molecules, the presence or absence of a spacer separating the capture molecules from the solid support of the microarray, as well as the length and the type of the spacer on the final combination of high specificity and high sensitivity of the method. The inventors showed that when long double-stranded target nucleotide molecules are hybridized to short capture molecules without a spacer, the assay is quite specific but not at all sensitive (i.e. giving false negative results). When long double-stranded target nucleotide molecules are hybridized to long capture molecules without a spacer, the assay is sensitive but not specific (i.e. giving false positive results).

Moreover, long, double-stranded target molecules cannot ordinarily be used with short capture molecules because the kinetics of hybridization will favor the re-annealing of the two long strands of the target molecule over annealing of one long target strand to the short capture molecule. However, Applicants unexpectedly discovered that full-length, double-stranded target molecules of 100 to 800 bases could be used in an assay with capture molecules of 15 to 40 nucleotides that also comprise an oligonucleotide spacer of at least 40 bases. When such a combination was used, the assay became both sensitive and specific (reducing both the false negative and false positive results). Furthermore, the kinetics of hybridization were sufficient to permit obtaining results in a very short time. Thus, the data presented in the Declaration unambiguously shows that the method as claimed is the most sensitive and specific when the conditions are as follows: long double-stranded target nucleotide molecules (100-800 bases), are hybridized to single-stranded capture molecules having a short specific sequence of about 15-40 nucleotides and an oligonucleotide spacer of at least 40 bases in length. Moreover, oligonucleotide spacers were unexpectedly superior to non-nucleotide spacers.

Guschin et al. do not use nor suggest using a polynucleotide spacer, and this reference describes fragmenting the target molecules into 40-base single-stranded sequences before applying the fragments to a microchip. Thus, Guschin fails to disclose the use of the "full-length" target or the "spacer comprising a nucleotide sequence" of the pending claims.

Bamdad describes using a conductive oligomer, which is not an oligonucleotide. The preferred length of the spacer is from about 6Å to about 100Å. Since each base in a single-stranded nucleic acid takes up approximately 7Å, the preferred length of the non-oligonucleotide spacers described by Bamdad, would only be as long as 1 to 14 nucleotides. Thus, the optimal spacer length of Bamdad is not within the range of the present invention (above 40 nucleotides). Therefore, the cited references in combination would not achieve the claimed invention, even if there were motivation to combine them. Moreover, it is entirely unexpected to achieve high sensitivity with short capture sequences and high specificity with long target sequences, both of which are achieved with good kinetics of reaction. The unexpected results further evidence the non-obviousness of the claimed invention.

As such, currently amended Claims 1, 2, 9, 10, 12, 13, 16, 17, 38, 40, 42, 44 and 45 are not obvious over the cited references and their rejection under 35 USC §103(a) should be withdrawn.

The Examiner has rejected Claims 12 and 44 under 35 USC §103(a) as being allegedly unpatentable over Guschin et al. (*Appl. Environ. Microbiol.* 1997 63:2397-2402) in view of Bamdad (USP 6,541,617) as applied to Claims 1, 2, 9, 10, 12, 13, 16, 17, 38, 40, 42, 44 and 45 above and further in view of Martineau et al. (*Antimicrob. Agents Chemother.* 2000 44:231-238). More specifically, the Examiner alleges that because Martineau et al. teach a method comprising amplifying and detecting antibiotic resistance genes, as well as bacterial 16S rRNA and *Staphylococcus aureus* and *Staphylococcus epidermidis* specific targets in multiplex PCR, it would have been obvious to combine this teaching with the method of Guschin et al. as modified by using a spacer of at least 40 bases in length as taught by Bamdad et al.

Martineau's disclosure of the use of a primer pair capable of amplifying multiple homologous genes (16S rDNA) from a variety of bacterial species does not provide motivation to combine arrays comprising covalently bound probes of the lengths recited in the claims which comprise a spacer of at least 40 nucleotides in length, and primer pairs capable of amplifying at least two of 4 homologous sequences in methods for detecting specific nucleotide sequences having a homology level higher than 30% with sequences from other organisms. As discussed above, Guschin et al. combined with Bamdad et al. do not disclose all the limitations of the claimed invention, and Apple *et al.* fails to correct the failure of Guschin et al. combined with Bamdad et al. to render the claimed invention obvious for the reasons addressed above. Therefore, dependent Claims 12 and 44 are also non-obvious.

The Examiner has rejected Claims 4, 14, 15, 17-23 under 35 U.S.C. §103(a) as being allegedly unpatentable over Guschin et al. (*Appl. Environ. Microbiol.* 1997 63:2397-2402) in view of Bamdad (USP 6,541,617) as applied to Claims 1, 2, 9, 10, 12, 13, 16, 17, 38, 40, 42, 44 and 45 above, and further in view of: Vannuffel et al. (WO 99/16780) - Claims 15 and 17; Boon et al. (USP 6,488,932) - Claim 18; Apple et al. (USP 5,451,512) - Claims 4, 14 and 19; Klein et al. (USP 6,255,059) - Claims 20 and 22; Murphy et al. (WO 94/05695) - Claim 21; and Waxman et al. (USP 6,207,648) – Claim 23. More specifically, the Examiner believes that because these additional references describe specific sequences belonging to a Mycobacteria family, MAGE family, HLA-A family, G gene family, cytochrome P450 isoforms family, dopamine or histamine receptors coupled to the G gene family, FemA gene of staphylococci species family, A gyrase family, sequences belonging to specific animal species or sequences belonging to genetically

modified organisms, it would have been obvious to combine these references with the teachings of Guschin et al.

The additional references fail to cure the primary references' lack of teaching or suggestion of the characteristics of the method according to the present invention as discussed above. Therefore, Applicant asserts that Claims 43, 48-54, 86, and 89-94 are non-obvious in view of the cited prior art, and respectfully requests withdrawal of their rejection under 35 U.S.C. §103(a).

CONCLUSION

In view of the foregoing, Applicants respectfully submit the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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By: 

Daniel Hart
Registration No. 40,637
Attorney of Record
Customer No. 20,995
(619) 235-8550

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062206